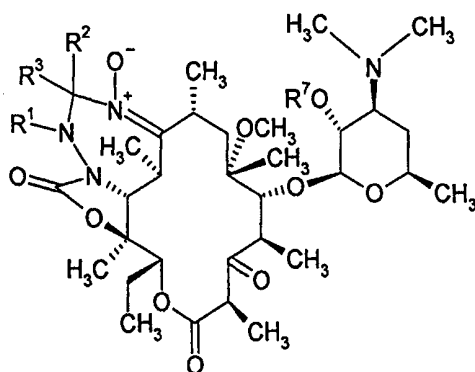




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07H 17/08, A61K 31/70	A1	(11) International Publication Number: WO 99/62920 (43) International Publication Date: 9 December 1999 (09.12.99)
<p>(21) International Application Number: PCT/IB99/00855</p> <p>(22) International Filing Date: 12 May 1999 (12.05.99)</p> <p>(30) Priority Data: 60/087,798 3 June 1998 (03.06.98) US</p> <p>(71) Applicant (for all designated States except US): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): WU, Yong-Jin [CA/US]; 36 Cardinal Road, East Lyme, CT 06333 (US).</p> <p>(74) Agents: SPIEGEL, Allen, J. et al.; Simpson, Alison, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	

(54) Title: TRICYCLIC 3-KETO DERIVATIVES OF 6-O-METHYLERYTHROMYCIN



(1)

(57) Abstract

The invention relates to compounds of formula (1) and to pharmaceutically acceptable salts thereof, wherein R⁷, R¹, R³ and R² are as defined herein. The invention also relates to pharmaceutical compositions containing the compounds of formula (1), methods of using said compounds of formula (1) in the treatment of infections, and methods of preparing said compounds of formula (1).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

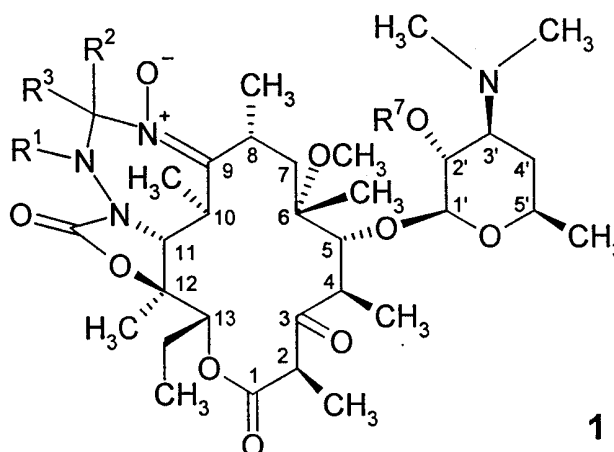
TRICYCLIC 3-KETO DERIVATIVES OF 6-O-METHYLERYTHROMYCINBackground Of The Invention

This invention relates to tricyclic 3-keto derivatives of 6-O-methylerythromycin A. The compounds of this invention are useful as antibiotic agents in mammals, including man, as well as in fish and birds. The compounds of the present invention are broad-spectrum macrolide antibiotics that are effective against infections caused by certain gram-positive and gram-negative bacteria as well as protozoa.

Macrolide antibiotics are known to be useful in the treatment of a broad spectrum of bacterial infections and protozoa infections in mammals, fish and birds. Such antibiotics include various derivatives of erythromycin A such as azithromycin which is commercially available and is referred to in United States patents 4,474,768 and 4,517,359, both of which are incorporated herein by reference in their entirety. Additional macrolides are referred to in U.S. patent application serial number 60/063676, filed October 29, 1997 (Yong-Jin Wu), U.S. application serial number 60/063161, filed October 29, 1997 (Yong-Jin Wu), U.S. application serial number 60/054866, filed August 6, 1997 (Hiroko Masamune, Yong-Jin Wu, Takushi Kaneko and Paul R. McGuirk), all of which are incorporated herein by reference in their entirety. Like azithromycin and other macrolide antibiotics, the novel macrolide compounds of the present invention possess activity against various bacterial infections and protozoa infections as described below.

Summary of the Invention

The present invention relates to compounds of the formula



and to pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from H, $-(CR^4R^5)_mR^6$, $-C(O)(CR^4R^5)_mR^6$, $-C(O)O(CR^4R^5)_mR^6$, $-C(O)NR^4(CR^4R^5)_mR^6$, wherein m is an integer ranging from 0 to 6 and both R^4 and R^5 may vary for each iteration where m is greater than 1;

each R² and R³ are independently selected from H and C₁-C₁₈ alkyl, wherein one or two carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N, and are optionally substituted by 1 to 3 substituents independently selected from the group consisting of -C(O)O(C₁-C₁₀)alkyl, -O(C₁-C₁₀)alkyl, C₁-C₁₀ alkanoyl, halo, nitro, cyano, C₁-C₁₀ alkyl, 4-10
5 membered heterocyclic, C₆-C₁₀ aryl, -NH(C₁-C₁₀)alkyl, -S(C₁-C₁₀ alkyl), -SO(C₁-C₁₀)alkyl, -SO₂(C₁-C₁₀)alkyl and -SO₂N(C₁-C₁₀)alkyl, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other;

each R⁴ and R⁵ are independently selected from H, halo and C₁-C₆ alkyl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and each
10 R⁴ and R⁵ may vary independently when m is greater than 1, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other; or

each R⁴ and R⁵ taken together with the carbon to which they are attached can form a 3-10 membered ring, wherein one or more carbons of said ring are optionally replaced by a heteroatom selected from O, S and N, and are optionally substituted by 1 to 3 substituents
15 independently selected from the group consisting of -C(O)O(C₁-C₁₀)alkyl, -O(C₁-C₁₀)alkyl, C₁-C₁₀ alkanoyl, halo, nitro, cyano, C₁-C₁₀ alkyl, 4-10 membered heterocyclic, C₆-C₁₀ aryl, -NH(C₁-C₁₀)alkyl, -N((C₁-C₁₀)alkyl)₂, -S(C₁-C₁₀)alkyl, -SO(C₁-C₁₀)alkyl, -SO₂(C₂(C₁-C₁₀)alkyl and -SO₂N(C₁-C₁₀)alkyl, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other;

R⁶ is (C₁-C₁₈)alkyl, a 4-10 membered heterocyclic or C₆-C₁₀ aryl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and said heterocyclic and aryl groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of -C(O)O(C₁-C₁₀)alkyl, -O(C₁-C₁₀)alkyl, C₁-C₁₀ alkanoyl, halo, nitro, cyano, (C₁-C₁₀) alkyl, -NH(C₁-C₁₀)alkyl, -N((C₁-C₁₀)alkyl)₂, -S(C₁-C₁₀ alkyl), -SO(C₁-C₁₀)alkyl,
25 -SO₂(C₁-C₁₀)alkyl and -SO₂N(C₁-C₁₀)alkyl, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other; and

R⁷ is H, -C(O)O(C₁-C₁₈)alkyl or -C(O)(C₁-C₁₈)alkyl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and wherein in the alkyl portion of said alkanoyl one or two carbons optionally may be replaced by a heteroatom selected
30 from O, S and N, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other.

More specific embodiments of this invention include compounds of formula 1 wherein R⁷ is H.

More specific embodiments of this invention include compounds of formula 1 wherein R³
35 is H.

More specific embodiments of this invention include compounds of formula 1 wherein $R^3=R^2=H$.

More specific embodiments of this invention include compounds of formula 1 wherein $R^3=R^2=R^7=H$.

- 5 Other more specific embodiments of this invention include compounds of formula 1 wherein R^2 is $(CH_2)_m R^6$, wherein m is an integer ranging from 0 to 6. Specific embodiments of compounds of formula 1 wherein R^2 is $(CH_2)_m R^6$ and wherein m is an integer ranging from 0 to 6 include such compounds wherein R^6 is quinolin-4-yl, quinolin-5-yl, quinolin-8-yl, 4-phenyl-1-imidazol-1-yl, 4-pyridin-3-yl-imidazol-1-yl, or imidazo(4,5-b)pyridin-3-yl. More specific
- 10 embodiments of this invention include compounds of formula 1 wherein R^2 is $(CH_2)_m R^6$ and m is 3. Specific embodiments of compounds of formula 1 wherein R^2 is $(CH_2)_m R^6$ and m is 3 include such compounds wherein R^6 is quinolin-4-yl, quinolin-5-yl, quinolin-8-yl, 4-phenyl-1-imidazol-1-yl, 4-pyridin-3-yl-imidazol-1-yl or imidazo(4,5-b)pyridin-3-yl.

Examples of preferred compounds of this invention include:

- 15 the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -quinolin-4-yl-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=7$ -methoxy-quinolin-4-yl)-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -benzimidazol-1-yl-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -indol-1-yl-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -indazol-1-yl-propyl;
- 20 the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -carbazol-1-yl-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(5-phenyl-1H-pyrrol-2-yl)-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(4-phenyl-imidazol-1-yl)-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(imidazo(4,5-b)pyridin-3-yl)-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(4-pyridin-3-yl-imidazol-1-yl)-propyl;
- 25 the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(3-(4-chlorophenyl)-(1,2,4)oxadiazol-5-yl)-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(3-(4-methoxyphenyl)-(1,2,4)oxadiazol-5-yl)-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(3-(4-pyridin-4-yl)-(1,2,4)oxadiazol-5-
- 30 yl)-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -benzotriazol-1-yl-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -benzotriazol-2-yl-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(1H-indol-3-yl)-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -pyridin-4-yl-propyl;
- 35 the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -pyridin-3-yl-propyl;
the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -pyridin-2-yl-propyl;

- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -phenylpropyl;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(2-methoxyphenyl)-propyl;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -furan-2-yl-propyl;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -thiophen-2-yl-propyl;
- 5 the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -pyrrol-1-yl-propyl;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(2-pyridin-3-yl-thiazol-4-yl)-propyl;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(2-phenyl-thiazol-5-yl)-propyl;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(2-phenyl-thiazol-5-yl)-propyl;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3$ -(4-phenyl-1H-imidazol-2-yl)-propyl;
- 10 and pharmaceutically acceptable salts of the foregoing compounds.

The invention also relates to a pharmaceutical composition for the treatment of a bacterial infection or protozoal infection in a mammal, fish, or bird which comprises a therapeutically effective amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

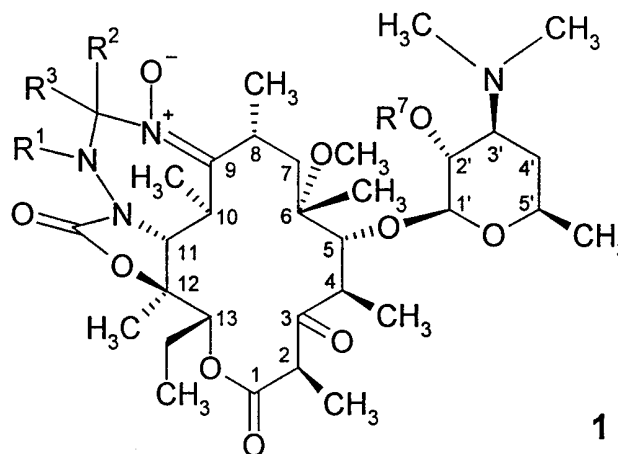
- 15 The invention also relates to a method of treating a bacterial infection or a protozoal infection in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of a compound of formula 1 or a pharmaceutically acceptable salt thereof.

The term "treatment", as used herein, unless otherwise indicated, includes the treatment
20 or prevention of a bacterial infection or protozoal infection as provided in the method of the present invention.

- As used herein, unless otherwise indicated, the term "bacterial infection(s)" or "protozoa infection" includes bacterial infections and protozoa infections that occur in mammals, fish and birds as well as disorders related to bacterial infections and protozoa infections that may be
25 treated or prevented by administering antibiotics such as the compounds of the present invention. Such bacterial infections and protozoa infections and disorders related to such infections include the following: pneumonia, otitis media, sinusitis, bronchitis, tonsillitis, and mastoiditis related to infection by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, or *Peptostreptococcus* spp.; pharyngitis, rheumatic fever, and
30 glomerulonephritis related to infection by *Streptococcus pyogenes*, Groups C and G streptococci, *Clostridium diphtheriae*, or *Actinobacillus haemolyticum*; respiratory tract infections related to infection by *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Chlamydia pneumoniae*; uncomplicated skin and soft tissue infections, abscesses and osteomyelitis, and puerperal fever related to infection by
35 *Staphylococcus aureus*, coagulase-positive staphylococci (i.e., *S. epidermidis*, *S. hemolyticus*, etc.), *Streptococcus pyogenes*, *Streptococcus agalactiae*, Streptococcal groups C-F (minute-

colony streptococci), viridans streptococci, *Corynebacterium minutissimum*, *Clostridium* spp., or *Bartonella henselae*; uncomplicated acute urinary tract infections related to infection by *Staphylococcus saprophyticus* or *Enterococcus* spp.; urethritis and cervicitis; and sexually transmitted diseases related to infection by *Chlamydia trachomatis*, *Haemophilus ducreyi*,
5 *Treponema pallidum*, *Ureaplasma urealyticum*, or *Neisseria gonorrhoeae*; toxin diseases related to infection by *S. aureus* (food poisoning and Toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by *Helicobacter pylori*; systemic febrile syndromes related to infection by *Borrelia recurrentis*; Lyme disease related to infection by *Borrelia burgdorferi*; conjunctivitis, keratitis, and dacrocystitis related to infection by *Chlamydia trachomatis*, *Neisseria*
10 *gonorrhoeae*, *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium*, or *Mycobacterium intracellulare*; gastroenteritis related to infection by *Campylobacter jejuni*; intestinal protozoa related to infection by *Cryptosporidium* spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to
15 infection by *Bordetella pertussis*; gas gangrene related to infection by *Clostridium perfringens* or *Bacteroides* spp.; and atherosclerosis related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae*. Bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in animals include the following: bovine respiratory disease related to infection by *P. haem.*, *P. multocida*, *Mycoplasma bovis*, or *Bordetella* spp.; cow enteric
20 disease related to infection by *E. coli* or protozoa (i.e., coccidia, cryptosporidia, etc.); dairy cow mastitis related to infection by *Staph. aureus*, *Strep. uberis*, *Strep. agalactiae*, *Strep. dysgalactiae*, *Klebsiella* spp., *Corynebacterium*, or *Enterococcus* spp.; swine respiratory disease related to infection by *A. pleuro.*, *P. multocida*, or *Mycoplasma* spp.; swine enteric disease related to infection by *E. coli*, *Lawsonia intracellularis*, *Salmonella*, or *Serpulina hyodysintertiae*; cow
25 footrot related to infection by *Fusobacterium* spp.; cow metritis related to infection by *E. coli*; cow hairy warts related to infection by *Fusobacterium necrophorum* or *Bacteroides nodosus*; cow pink-eye related to infection by *Moraxella bovis*; cow premature abortion related to infection by protozoa (i.e. neosporium); urinary tract infection in dogs and cats related to infection by *E. coli*; skin and soft tissue infections in dogs and cats related to infection by *Staph. epidermidis*, *Staph.*
30 *intermedius*, *coagulase neg. Staph.* or *P. multocida*; and dental or mouth infections in dogs and cats related to infection by *Alcaligenes* spp., *Bacteroides* spp., *Clostridium* spp., *Enterobacter* spp., *Eubacterium*, *Peptostreptococcus*, *Porphyromonas*, or *Prevotella*. Other bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in accord with the method of the present invention are referred to in J. P. Sanford et al., "The Sanford Guide To Antimicrobial Therapy," 26th Edition, (Antimicrobial Therapy, Inc.,
35 1996).

The invention also relates to a method of preparing a compound of the formula



and to pharmaceutically acceptable salts thereof, wherein:

- 5 R^1 is selected from H, $-(CR^4R^5)_mR^6$, $-C(O)(CR^4R^5)_mR^6$, $-C(O)O(CR^4R^5)_mR^6$, $-C(O)NR^4(CR^4R^5)_mR^6$, wherein m is an integer ranging from 0 to 6 and both R^4 and R^5 may vary for each iteration where m is greater than 1;

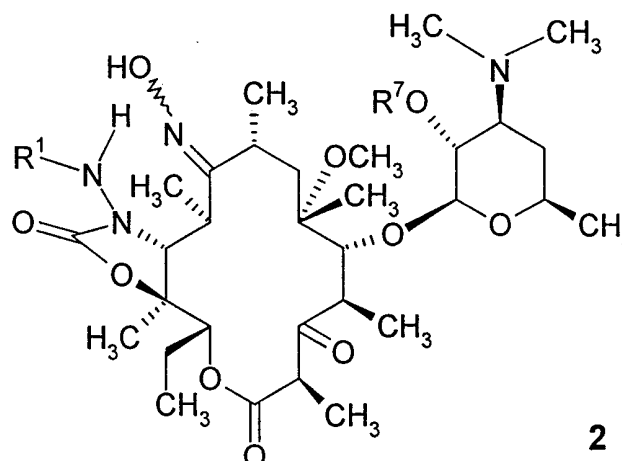
- each R^2 and R^3 are independently selected from H and C_1 - C_{18} alkyl, wherein one or two carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N, and are
 10 optionally substituted by 1 to 3 substituents independently selected from the group consisting of $-C(O)O(C_1-C_{10})$ alkyl, $-O(C_1-C_{10})$ alkyl, C_1 - C_{10} alkanoyl, halo, nitro, cyano, C_1 - C_{10} alkyl, 4-10 membered heterocyclic, C_6 - C_{10} aryl, $-NH(C_1-C_{10})$ alkyl, $-S(C_1-C_{10})$ alkyl, $-SO(C_1-C_{10})$ alkyl, $-SO_2(C_1-C_{10})$ alkyl and $-SO_2N(C_1-C_{10})$ alkyl, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other;

- 15 each R^4 and R^5 are independently selected from H, halo and C_1 - C_6 alkyl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and each R^4 and R^5 may vary independently when m is greater than 1, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other; or

- each R^4 and R^5 taken together with the carbon to which they are attached can form a 3-
 20 10 membered ring, wherein one or more carbons of said ring are optionally replaced by a heteroatom selected from O, S and N, and are optionally substituted by 1 to 3 substituents independently selected from the group consisting of $-C(O)O(C_1-C_{10})$ alkyl, $-O(C_1-C_{10})$ alkyl, C_1 - C_{10} alkanoyl, halo, nitro, cyano, C_1 - C_{10} alkyl, 4-10 membered heterocyclic, C_6 - C_{10} aryl, $-NH(C_1-C_{10})$ alkyl, $-N((C_1-C_{10})alkyl)_2$, $-S(C_1-C_{10})$ alkyl, $-SO(C_1-C_{10})$ alkyl, $-SO_2(C_2(C_1-C_{10})alkyl)$ and
 25 $-SO_2N(C_1-C_{10})$ alkyl, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other;

R⁶ is (C₁-C₁₈)alkyl, a 4-10 membered heterocyclic or C₆-C₁₀ aryl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and said heterocyclic and aryl groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of -C(O)O(C₁-C₁₀)alkyl, -O(C₁-C₁₀)alkyl, C₁-C₁₀ alkanoyl, halo, nitro, cyano, (C₁-C₁₀) alkyl, -NH(C₁-C₁₀)alkyl, -N((C₁-C₁₀)alkyl)₂, -S(C₁-C₁₀ alkyl), -SO(C₁-C₁₀)alkyl, -SO₂(C₁-C₁₀)alkyl and -SO₂N(C₁-C₁₀)alkyl, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other; and

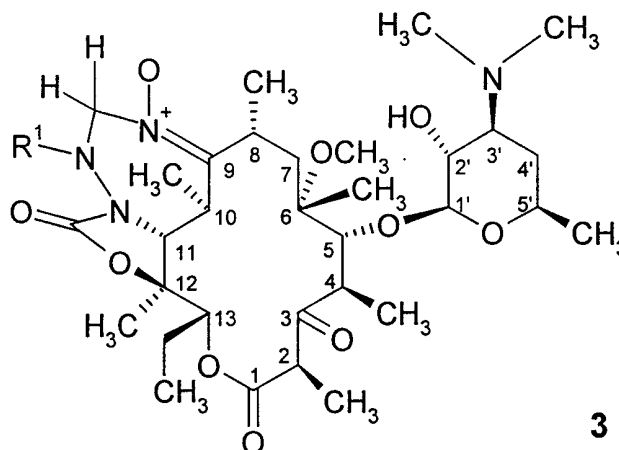
R⁷ is H, -C(O)O(C₁-C₁₈)alkyl or -C(O)(C₁-C₁₈)alkyl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and wherein in the alkyl portion of said alkanoyl one or two carbons optionally may be replaced by a heteroatom selected from O, S and N, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other, which comprises treating a compound of the formula



wherein R⁷ and R¹ are as defined above, with a compound of the formula R³R²C=O, wherein R³ and R² are as defined for the compound of formula 1, in the presence of an acid. An example of a preferred compound of the formula R³R²C=O is CH₂O. Examples of suitable acids include, for example, acetic acid, formic acid, para-toluene sulfonic acid and propanoic acid. The acid may be in the presence of a suitable solvent, such as for example, CH₂Cl₂, C₆H₆, CHCl₃, acetonitrile, dimethylformamide, tetrahydrofuran, dioxane and dichloroethane.

The compound of formula 2 can be prepared as described in U.S. patent application serial no. 60/049349, filed June 11, 1997 (Yong-Jin Wu), and in corresponding International Application no. WO 9856800, published December 17, 1998, which is herein incorporated by reference in its entirety.

The present invention further relates to a compound of the formula



and to pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from H, $-(CR^4R^5)_mR^6$, $-C(O)(CR^4R^5)_mR^6$, $-C(O)O(CR^4R^5)_mR^6$,

- 5 $-C(O)NR^4(CR^4R^5)_mR^6$, wherein m is an integer ranging from 0 to 6 and both R^4 and R^5 may vary for each iteration where m is greater than 1;

each R^4 and R^5 are independently selected from H, halo and C_1 - C_6 alkyl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and each R^4 and R^5 may vary independently when m is greater than 1, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other; or

each R^4 and R^5 taken together with the carbon to which they are attached can form a 3-10 membered ring, wherein one or more carbons of said ring are optionally replaced by a heteroatom selected from O, S and N, and are optionally substituted by 1 to 3 substituents independently selected from the group consisting of $-C(O)O(C_1-C_{10})$ alkyl, $-O(C_1-C_{10})$ alkyl, C_1-C_{10} alkanoyl, halo, nitro, cyano, C_1-C_{10} alkyl, 4-10 membered heterocyclic, C_6-C_{10} aryl, $-NH(C_1-C_{10})$ alkyl, $-N((C_1-C_{10})alkyl)_2$, $-S(C_1-C_{10})alkyl$, $-SO(C_1-C_{10})alkyl$, $-SO_2(C_2(C_1-C_{10})alkyl)$ and $-SO_2N(C_1-C_{10})alkyl$, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other; and

R^6 is (C_1-C_{18}) alkyl, a 4-10 membered heterocyclic or C_6-C_{10} aryl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and said heterocyclic and aryl groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of $-C(O)O(C_1-C_{10})$ alkyl, $-O(C_1-C_{10})$ alkyl, C_1-C_{10} alkanoyl, halo, nitro, cyano, (C_1-C_{10}) alkyl, $-NH(C_1-C_{10})$ alkyl, $-N((C_1-C_{10})alkyl)_2$, $-S(C_1-C_{10})$ alkyl, $-SO(C_1-C_{10})alkyl$, $-SO_2(C_1-C_{10})alkyl$ and $-SO_2N(C_1-C_{10})alkyl$, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other.

groups include benzo-fused ring systems and ring systems substituted with one or more oxo moieties. An example of a 5 membered heterocyclic group is thiazolyl, and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, piperidino, morpholino, thiomorpholino and piperazinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl and thiazolyl. In general, acceptable 4-10 membered heterocyclic groups include those derived from one of the following: furan, thiophene, 2H-pyrrole, pyrrole, 2-pyrroline, 3-pyrroline, pyrrolidine, 1,3-dioxolane, oxazole, thiazole, imidazole, 2-imidazole, imidazolidine, pyrazole, 2-pyrazoline, pyrazolidine, isoxazole, isothiazole, 1,2,3-oxadiazole, 1,2,3-triazole, 1,3,4-thiadiazole, 2H-pyran, 4H-pyran, pyridine, piperidine, 1,4-dioxane, 1,3-dioxane, morpholine, 1,4-dithiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, 1,3,5-triazine, 1,3,5-trithiane, indolizine, indole, isoindole, 3H-indole, indoline, benzofuran, benzothiophene, 1H-indazole, benzimidazole, benzthiazole, purine, 4H-quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine, quinuclidine, carbazole, acridine, phenazine, phenothiazine, phenoxazine, tetrazole, thietane and azetidene.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formula 1. The compounds of formula 1 that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of formula 1 are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula 1 that are acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts and particularly, the sodium and potassium salts.

The present invention also includes all radiolabelled forms of the compounds of formula 1, and pharmaceutically acceptable salts thereof, wherein the radiolabel is selected from ^3H , ^{11}C and ^{14}C . Such radiolabelled compounds are useful as research or diagnostic tools.

Certain compounds of formula 1 may have asymmetric centers and therefore exist in different enantiomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of formula 1 and mixtures thereof. The compounds of formula 1 may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

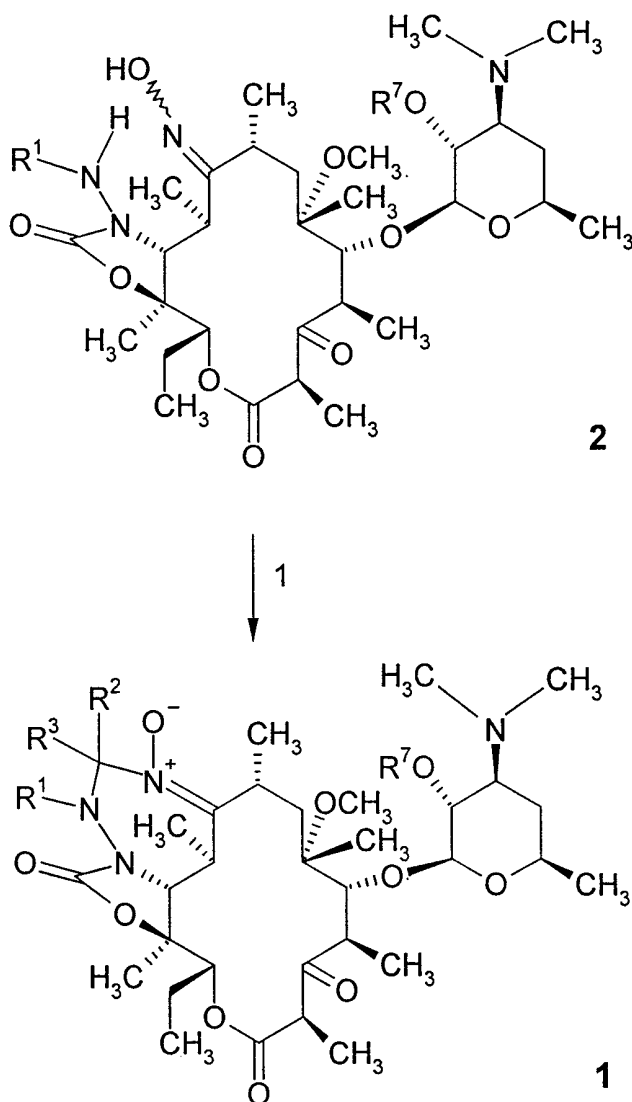
5

Detailed Description of the Invention

The preparation of the compounds of the present invention is illustrated in the following Scheme.

Scheme

5



The Scheme illustrates the general synthesis of the compounds of the present invention. In the Scheme, the starting compound of formula 2 can be prepared as described in U.S. patent application serial no. 60/049349, filed June 11, 1997 (Yong-Jin Wu), and in corresponding International Application no. WO 9856800, published December 17, 1998, which are herein
5 incorporated by reference in its entirety.

The tricyclic nitron of the compound of formula 1 can be prepared by treating the starting compound of formula 2 with a compound of the formula $R^3R^2C=O$, wherein R^3 and R^2 are defined as specified in the compound of formula 1, in the presence of an acid such as formic acid, acetic acid, para-toluenesulfonic acid or propionic acid in a solvent such as $CHCl_3$,
10 chloroform, benzene, acetonitrile, dimethylformamide (DMF), tetrahydrofuran (THF), dioxane or dichloroethane, at a temperature within the range from about 10 to about 90°C for a period of about 1 to 18 hours.

The compounds of the present invention may have asymmetric carbon atoms. Such diastereomeric mixtures can be separated into their individual diastereomers on the basis of their
15 physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including
20 diastereomer mixtures and pure enantiomers are considered as part of the invention.

The compounds of formula 1 that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially
25 isolate the compound of formula 1 from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or
30 organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of the formula 1 that are acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali
35 metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts may be prepared by conventional techniques. The chemical bases which are used as reagents to

prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula 1. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The activity of the compounds of the present invention against bacterial and protozoa pathogens is demonstrated by the compound's ability to inhibit growth of defined strains of human (Assay I) or animal (Assays II and III) pathogens.

Assay I

Assay I, described below, employs conventional methodology and interpretation criteria and is designed to provide direction for chemical modifications that may lead to compounds that circumvent defined mechanisms of macrolide resistance. In Assay I, a panel of bacterial strains is assembled to include a variety of target pathogenic species, including representatives of macrolide resistance mechanisms that have been characterized. Use of this panel enables the chemical structure/activity relationship to be determined with respect to potency, spectrum of activity, and structural elements or modifications that may be necessary to obviate resistance mechanisms. Bacterial pathogens that comprise the screening panel are shown in the table below. In many cases, both the macrolide-susceptible parent strain and the macrolide-resistant strain derived from it are available to provide a more accurate assessment of the compound's ability to circumvent the resistance mechanism. Strains that contain the gene with the designation of *ermA/ermB/ermC* are resistant to macrolides, lincosamides, and streptogramin B antibiotics due to modifications (methylation) of 23S rRNA molecules by an Erm methylase, thereby generally prevent the binding of all three structural classes. Two types of macrolide efflux have been described; *msrA* encodes a component of an efflux system in staphylococci that prevents the entry of macrolides and streptogramins while *mefA/E* encodes a transmembrane protein that appears to efflux only macrolides. Inactivation of macrolide antibiotics can occur and can be mediated by either a phosphorylation of the 2'-hydroxyl (*mph*) or by cleavage of the macrocyclic lactone (esterase). The strains may be characterized using conventional polymerase chain reaction (PCR) technology and/or by sequencing the resistance determinant. The use of PCR technology in this application is described in J. Sutcliffe et al., "Detection Of Erythromycin-Resistant Determinants By PCR", *Antimicrobial Agents and Chemotherapy*, 40(11),

- 2562-2566 (1996). The antibacterial assay is performed in microtiter trays and interpreted according to Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition; Approved Standard, published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines; the minimum inhibitory concentration (MIC) is used to compare strains. acr
- 5 AB or acr AB-like indicates that an intrinsic multidrug efflux pump exists in the strain. Compounds are initially dissolved in dimethylsulfoxide (DMSO) as 40 mg/ml stock solutions.

Strain Designation	Macrolide Resistance Mechanism(s)
Staphylococcus aureus 1116	susceptible parent
Staphylococcus aureus 1117	ermB
Staphylococcus aureus 0052	susceptible parent
Staphylococcus aureus 1120	ermC
Staphylococcus aureus 1032	msrA, mph, esterase
Staphylococcus hemolyticus 1006	msrA, mph
Streptococcus pyogenes 0203	susceptible parent
Streptococcus pyogenes 1079	ermB
Streptococcus pyogenes 1062	susceptible parent
Streptococcus pyogenes 1061	ermB
Streptococcus pyogenes 1064	mefA
Streptococcus agalactiae 1024	susceptible parent
Streptococcus agalactiae 1023	ermB
Streptococcus pneumoniae 1016	susceptible
Streptococcus pneumoniae 1046	ermB
Streptococcus pneumoniae 1095	ermB
Streptococcus pneumoniae 1175	mefE
Haemophilus influenzae 0085	susceptible; acr AB-like
Haemophilus influenzae 0131	susceptible; acr AB-like
Moraxella catarrhalis 0040	susceptible
Moraxella catarrhalis 1055	erythromycin intermediate resistance
Escherichia coli 0266	susceptible; acr AB
Haemophilus influenzae 1100	susceptible; acr AB-like

- Assay II is utilized to test for activity against *Pasteurella multocida* and Assay III is utilized
- 10 to test for activity against *Pasteurella haemolytica*.

Assay II

This assay is based on the liquid dilution method in microliter format. A single colony of *P. multocida* (strain 59A067) is inoculated into 5 ml of brain heart infusion (BHI) broth. The test compounds are prepared by solubilizing 1 mg of the compound in 125 μ l of dimethylsulfoxide (DMSO). Dilutions of the test compound are prepared using uninoculated BHI broth. The concentrations of the test compound used range from 200 μ g/ml to 0.098 μ g/ml by two-fold serial dilutions. The *P. multocida* inoculated BHI is diluted with uninoculated BHI broth to make a 10^4 cell suspension per 200 μ l. The BHI cell suspensions are mixed with respective serial dilutions of the test compound, and incubated at 37°C for 18 hours. The minimum inhibitory concentration (MIC) is equal to the concentration of the compound exhibiting 100% inhibition of growth of *P. multocida* as determined by comparison with an uninoculated control.

Assay III

This assay is based on the agar dilution method using a Steers Replicator. Two to five colonies isolated from an agar plate are inoculated into BHI broth and incubated overnight at 37°C with shaking (200 rpm). The next morning, 300 μ l of the fully grown *P. haemolytica* preculture is inoculated into 3 ml of fresh BHI broth and is incubated at 37°C with shaking (200 rpm). The appropriate amounts of the test compounds are dissolved in ethanol and a series of two-fold serial dilutions are prepared. Two ml of the respective serial dilution is mixed with 18 ml of molten BHI agar and solidified. When the inoculated *P. haemolytica* culture reaches 0.5 McFarland standard density, about 5 μ l of the *P. haemolytica* culture is inoculated onto BHI agar plates containing the various concentrations of the test compound using a Steers Replicator and incubated for 18 hours at 37°C. Initial concentrations of the test compound range from 100-200 μ g/ml. The MIC is equal to the concentration of the test compound exhibiting 100% inhibition of growth of *P. haemolytica* as determined by comparison with an uninoculated control.

The in vivo activity of the compounds of formula (I) can be determined by conventional animal protection studies well known to those skilled in the art, usually carried out in mice.

Mice are allotted to cages (10 per cage) upon their arrival, and allowed to acclimate for a minimum of 48 hours before being used. Animals are inoculated with 0.5 ml of a 3×10^3 CFU/ml bacterial suspension (*P. multocida* strain 59A006) intraperitoneally. Each experiment has at least 3 non-medicated control groups including one infected with 0.1X challenge dose and two infected with 1X challenge dose; a 10X challenge data group may also be used. Generally, all mice in a given study can be challenged within 30-90 minutes, especially if a repeating syringe (such as a Cornwall® syringe) is used to administer the challenge. Thirty minutes after challenging has begun, the first compound treatment is given. It may be necessary for a second person to begin compound dosing if all of the animals have not been challenged at the end of 30 minutes. The routes of administration are subcutaneous or oral doses. Subcutaneous doses are administered into the

loose skin in the back of the neck whereas oral doses are given by means of a feeding needle. In both cases, a volume of 0.2 ml is used per mouse. Compounds are administered 30 minutes, 4 hours, and 24 hours after challenge. A control compound of known efficacy administered by the same route is included in each test. Animals are observed daily, and the number of survivors in
5 each group is recorded. The *P. multocida* model monitoring continues for 96 hours (four days) post challenge.

The PD_{50} is a calculated dose at which the compound tested protects 50% of a group of mice from mortality due to the bacterial infection which would be lethal in the absence of drug treatment.

10 The compounds of formula 1 and their pharmaceutically acceptable salts (hereinafter referred to, collectively, as "the active compounds of this invention") may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining the active
15 compounds of this invention can then be readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various
20 disintegrants such as starch, methylcellulose, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high
25 molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions containing an active compound of this invention or a
30 pharmaceutically acceptable salt thereof in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by
35 standard techniques known to those skilled in the art.

To implement the methods of this invention, an effective dose of an active compound of this invention is administered to a susceptible or infected animal (including mammals, fish and birds) by parenteral (i.v., i.m. or s.c.), oral, or rectal routes, or locally as a topical application to the skin and/or mucous membranes. The route of administration will depend on the mammal, fish or bird that is being treated. The effective dose will vary with the severity of the disease, and the age, weight and condition of the animal. However, the daily dose will usually range from about 0.25 to about 150 mg/kg body weight of the patient to be treated, preferably from about 0.25 to about 25 mg/kg.

The Examples provided below illustrate specific embodiments of the invention, but the invention is not limited in scope to the Examples specifically exemplified.

10

Example 1

Compound of formula 1: R²=R³=R⁷=H, R¹=phenylbutyl

To a solution of 9-deoxo-9-hydroxyimino-11-deoxy-5-O-desosaminy-11-(3-phenylbutyl)hydrazo-6-O-methyl-3-oxoerythronolide A, 11,12-carbamate (formula 2, R₁=H, R₂=phenylbutyl) (50 mg, 0.06 mmol) in CHCl₃ (1 mL) was added 37% aqueous CH₂O (25 μL) followed by HCO₂H (23 μL). The resulting solution was heated at 65°C for 2 hours. The reaction was diluted with saturated NaHCO₃, and CH₂Cl₂ was added. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by preparative TLC (89% CH₂Cl₂-9% MeOH-1% NH₃·H₂O) to afford the title compound as a white solid.

¹H NMR (400 MHz, CDCl₃) δ: 7.28-7.08 (5H, m), 5.36 (1H, d, J = 14.4 Hz), 4.91 (1H, dd, J = 10.8 and 2.4 Hz), 4.79 (1H, d, J = 14.4 Hz), 4.34 (1H, d, J = 8.0 Hz), 4.28 (1H, d, J = 7.2 Hz), 3.96 (1H, s), 3.83 (1H, q, J = 6.8 Hz), 3.19 (1H, dd, J = 7.6 and 10.0 Hz), 3.03 (1H, dq, J = 7.6 and 8.0 Hz), 2.79 (3H, s), 2.62 (1H, q, J = 6.8 Hz), 2.60 (2H, t, J = 7.2 Hz), 2.47 (1H, dt, J = 11.2 and 3.6 Hz), 2.27 (6H, s), 1.52 (3H, s), 1.46 (3H, s), 1.35 (3H, d, J = 6.8 Hz), 1.30 (3H, d, J = 7.6 Hz), 1.29 (3H, d, J = 7.6 Hz), 1.23 (3H, d, J = 6.4 Hz), 0.99 (3H, d, J = 7.2 Hz), 0.82 (3H, t, J = 7.6 Hz),

Exact mass calcd. for C₄₂H₆₇N₄O₁₀ (M+H): 787.4867; found: 787.4863.

Example 2

30

Compound of formula 1: R²=R³=R⁷=H, R¹=3-quinolin-4-yl-propyl

To a solution of 9-deoxo-9-hydroxyimino-11-deoxy-5-O-desosaminy-11-(3-quinolin-4-yl-propyl)hydrazo-6-O-methyl-3-oxoerythronolide A, 11,12-carbamate (formula 2, R₁=H, R₂=3-quinolin-4-yl-propyl) (187 mg, 0.23 mmol) in CHCl₃ (11 mL) was added 37% aqueous CH₂O (88 μL) followed by HCO₂H (81 μL). The resulting solution was heated at 65°C for 2 hour. The reaction was diluted with saturated NaHCO₃, and CH₂Cl₂ was added. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were

35

washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by preparative TLC (89% CH_2Cl_2 -9% MeOH -1% $\text{NH}_3\cdot\text{H}_2\text{O}$) to afford the title compound as a white solid (121 mg).

^1H NMR (400 MHz, CDCl_3) δ : 8.76 (1H, d, $J = 4.4$ Hz), 8.10 (1H, d, $J = 8.4$ Hz), 8.07 (1H, d, $J = 8.8$ Hz), 7.66 (br. t, $J = 7.2$ Hz), 7.50 (1H, br. t, $J = 7.2$ Hz), 7.27 (1H, d, $J = 4.8$ Hz), 5.54 (1H, d, $J = 14.4$ Hz), 4.78 (1H, d, $J = 14.8$ Hz), 3.84 (1H, q, $J = 6.8$ Hz), 2.80 (3H, s), 2.30 (6H, s), 2.53 (3H, s), 1.47 (3H, s), 1.35 (3H, d, $J = 7.2$ Hz), 1.33 (3H, d, $J = 7.6$ Hz), 1.29 (3H, d, $J = 7.2$ Hz), 1.23 (3H, d, $J = 6.0$ Hz), 0.99 (3H, d, $J = 7.2$ Hz), and 0.77 (3H, t, $J = 7.6$ Hz).

^{13}C NMR (100 MHz, CDCl_3) δ : 203.58, 169.98, 157.63, 154.66, 150.11, 148.25, 147.95, 130.02, 129.01, 127.53, 126.34, 123.73, 121.05, 85.08, 81.07, 78.87, 77.78, 76.61, 70.27, 69.53, 65.89, 56.67, 51.49, 50.93, 50.65, 47.56, 40.23 (2C), 38.30, 31.07, 28.86, 28.35, 28.23, 28.17, 21.76, 21.17, 20.69, 18.82, 15.42, 14.72, 13.47, 12.55, and 10.37.

Exact mass calcd. for $\text{C}_{42}\text{H}_{67}\text{N}_4\text{O}_{10}$ (M+H): 824.4810; found: 824.4796.

Example 3

15 Compound of formula 1: $\text{R}^2=\text{R}^3=\text{R}^7=\text{H}$, $\text{R}^1=3\text{-(4-phenyl-imidazol-1-yl)-propyl}$

To a solution of 9-deoxo-9-hydroxyimino-11-deoxy-5-O-desosaminyl-11-(3-(4-phenyl-imidazol-1-yl)-propyl)hydrazo-6-O-methyl-3-oxoerythronolide A, 11,12-carbamate (formula 2, $\text{R}_1=\text{H}$, $\text{R}_2=3\text{-(4-phenyl-imidazol-1-yl)-propyl}$) (15 mg, 0.02 mmol) in CHCl_3 (1 mL) was added 37% aqueous CH_2O (7 μL) followed by HCO_2H (7 μL). The resulting solution was heated at 65°C for 20 hours. The reaction was diluted with saturated NaHCO_3 , and CH_2Cl_2 was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by preparative TLC (89% CH_2Cl_2 -9% MeOH -1% $\text{NH}_3\cdot\text{H}_2\text{O}$) to afford the title compound as a white solid (13 mg).

25 ^1H NMR (400 MHz, CDCl_3) δ : 7.75-7.15 (7H), 5.51 (1H, d, $J = 14.8$ Hz), 4.86 (1H, dd, $J = 1.6$ and 10.4 Hz), 4.71 (1H, d, $J = 14.8$ Hz), 4.32 (1H, d, $J = 8.4$ Hz), 4.27 (1H, d, $J = 7.2$ Hz), 3.93 (1H, s), 3.83 (1H, q, $J = 6.8$ Hz), 2.76 (3H, s), 2.31 (6H, s), 1.53 (3H, s), 1.45 (3H, s), 1.34 (3H, d, $J = 6.8$ Hz), 1.32 (3H, $J = 6.8$ Hz), 1.28 (3H, d, $J = 7.6$ Hz), 1.23 (3H, d, $J = 6.0$ Hz), 0.98 (3H, d, $J = 7.2$ Hz) and 0.80 (3H, t, $J = 7.2$ Hz).

30 Exact mass calcd. for $\text{C}_{44}\text{H}_{67}\text{N}_6\text{O}_{10}$ (M+H): 839.4914; found: 839.4904.

Example 4

Compound of formula 1: $\text{R}^2=\text{R}^3=\text{R}^7=\text{H}$, $\text{R}^1=3\text{-(2-methoxyphenyl)-propyl}$

To a solution of 9-deoxo-9-hydroxyimino-11-deoxy-5-O-desosaminyl-11-(3-(2-methoxyphenyl)-propyl)hydrazo-6-O-methyl-3-oxoerythronolide A, 11,12-carbamate (formula 2, 35 $\text{R}_1=\text{H}$, $\text{R}_2=3\text{-(2-methoxyphenyl)-propyl}$) (15 mg, 0.02 mmol) in CHCl_3 (1 mL) was added 37% aqueous CH_2O (7 μL) followed by HCO_2H (7 μL). The resulting solution was heated at 65°C for 2

hours. The reaction was diluted with saturated NaHCO_3 , and CH_2Cl_2 was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by preparative TLC (89% CH_2Cl_2 -9% MeOH -1% $\text{NH}_3\cdot\text{H}_2\text{O}$) to afford the title compound as a white solid (163 mg).

^1H NMR (400 MHz, CDCl_3) δ : 7.13 (2H), 6.79 (2H), 5.48 (1H, d, $J = 14.8$ Hz), 4.95 (1H, dd, $J = 2.4$ and 10.8 Hz), 4.79 (1H, d, $J = 14.8$ Hz), 4.32 (1H, d, $J = 7.6$ Hz), 4.29 (1H, d, $J = 7.2$ Hz), 3.98 (1H, s), 3.76 (3H, s), 2.78 (3H, s), 2.33 (6H, s), 1.52 (3H, s), 1.45 (3H, s), 1.35 (3H, d, $J = 6.8$ Hz), 1.31 (3H, d, $J = 6.8$ Hz), 1.29 (3H, d, $J = 7.6$ Hz), 1.24 (3H, d, $J = 6.4$ Hz), 0.99 (3H, d, $J = 6.8$ Hz) and 0.83 (3H, t, $J = 7.6$ Hz).

MS: m/z 803 (M+H).

Example 5

Compound of formula 1: $\text{R}^2=\text{R}^3=\text{R}^7=\text{H}$, $\text{R}^1=3\text{-furan-2-yl-propyl}$

To a solution of 9-deoxo-9-hydroxyimino-11-deoxy-5-O-desosaminy-11-(3-furan-2-yl-propyl)hydrazo-6-O-methyl-3-oxoerythronolide A, 11,12-carbamate (formula 2, $\text{R}_1=\text{H}$, $\text{R}_2=3\text{-furan-2-yl-propyl}$ (15 mg, 0.02 mmol) in CHCl_3 (1 mL) was added 37% aqueous CH_2O (7 μL) followed by HCO_2H (7 μL). The resulting solution was heated at 65°C for 2 hours. The reaction was diluted with saturated NaHCO_3 , and CH_2Cl_2 was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by preparative TLC (89% CH_2Cl_2 -9% MeOH -1% $\text{NH}_3\cdot\text{H}_2\text{O}$) to afford the title compound as a white solid.

^1H NMR (400 MHz, CDCl_3) δ : 7.25 (1H), 6.21 (1H), 5.98 (1H), 5.47 (1H, d, $J = 14.4$ Hz), 4.93 (1H, dd, $J = 2.0$ and 10.4 Hz), 4.77 (1H, d, $J = 14.4$ Hz), 4.32 (1H, d, $J = 7.6$ Hz), 4.27 (1H, d, $J = 7.2$ Hz), 3.96 (1H, s), 3.83 (1H, q, $J = 6.8$ Hz), 3.17 (1H, dd, $J = 7.2$ and 10.0 Hz), 2.77 (3H, s), 2.25 (6H, s), 1.52 (3H, s), 1.46 (3H, s), 1.35 (2H, d, $J = 6.8$ Hz), 1.31 (3H, d, $J = 6.8$ Hz), 1.29 (3H, d, $J = 6.8$ Hz), 1.23 (3H, d, $J = 6.0$ Hz), 0.98 (3H, d, $J = 6.8$ Hz), and 0.85 (3H, t, $J = 7.2$ Hz).

MS: m/z 763 (M+H).

Example 6

Compound of formula 1: $\text{R}^2=\text{R}^3=\text{R}^7=\text{H}$, $\text{R}^2=3\text{-benzoimidazol-1-yl-propyl}$

To a solution of 9-deoxo-9-hydroxyimino-11-deoxy-5-O-desosaminy-11-(3-benzoimidazol-1-yl-propyl)hydrazo-6-O-methyl-3-oxoerythronolide A, 11,12-carbamate (formula 2, $\text{R}_1=\text{H}$, $\text{R}_2=3\text{-benzoimidazol-1-yl-propyl}$ (15 mg, 0.02 mmol) in CHCl_3 (1 mL) was added 37% aqueous CH_2O (7 μL) followed by HCO_2H (7 μL). The resulting solution was heated at 65°C for 2 hours. The reaction was diluted with saturated NaHCO_3 , and CH_2Cl_2 was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was

purified by preparative TLC (89% CH₂Cl₂-9% MeOH-1% NH₃•H₂O) to afford the title compound as a white solid.

¹H NMR (400 MHz, CDCl₃) δ: 7.94 (1H, s), 7.77 (1H), 7.46 (1H), 7.24 (2H), 5.52 (1H, d, J = 14.4 Hz), 4.90 (1H, dd, J = 1.6 and 10.8 Hz), 4.63 (1H, d, J = 14.4 Hz), 4.31 (1H, d, J = 8.0 Hz),
5 4.29 (1H, d, J = 7.2 Hz), 3.94 (1H, s), 3.83 (1H, q, J = 6.8 Hz), 2.74 (3H, s), 2.41 (6H, s), 1.54 (3H, s), 1.43 (3H, s), 1.33 (6H, d, J = 6.8 Hz), 1.28 (3H, d, J = 7.6 Hz), 1.24 (3H, d, J = 6.0 Hz), 0.98 (3H, d, J = 7.2 Hz), and 0.82 (3H, t, J = 7.2 Hz).

MS: m/z 813 (M+H).

Example 7

10 Compound of formula 1: R²=R³=R⁷=H, R¹=3-indazol-1-yl-propyl

To a solution of 9-deoxy-9-hydroxyimino-11-deoxy-5-O-desosaminy-11-(3-indazol-1-yl-propyl)hydrazo-6-O-methyl-3-oxoerythronolide A, 11,12-carbamate (formula 2, R₁=H, R₂=3-indazol-1-yl-propyl) (19 mg, 0.02 mmol) in CHCl₃ (1 mL) was added 37% aqueous CH₂O (9 μL) followed by HCO₂H (8 μL). The resulting solution was heated at 65°C for 2 hours. The reaction
15 was diluted with saturated NaHCO₃, and CH₂Cl₂ was added. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by preparative TLC (89% CH₂Cl₂-9% MeOH-1% NH₃•H₂O) to afford the title compound as a white solid.

20 ¹H NMR (400 MHz, CDCl₃) δ: 7.97 (1H, s), 7.66 (1H, d, J = 7.6 Hz), 7.65 (1H, d, J = 8.0 Hz), 7.31 (1H, br. t, J = 6.0 Hz), 7.07 (1H, br. t, J = 6.0 Hz), 5.44 (1H, d, J = 14.4 Hz), 4.92 (1H, dd, J = 2.4 and 10.4 Hz), 4.43 (1H, d, J = 14.4 Hz), 4.30 (1H, t, J = 8.0 Hz), 3.95 (1H, s), 3.81 (1H, q, J = 6.8 Hz), 2.71 (3H, s), 2.43 (6H, s), 1.54 (3H, s), 1.39 (3H, s), 1.34 (3H, d, J = 6.8 Hz), 1.33 (3H, d, J = 6.8 Hz), 1.27 (3H, d, J = 7.6 Hz), 1.24 (3H, d, J = 6.0 Hz), 0.97 (3H, d, J = 6.8
25 Hz) and 0.82 (3H, t, J = 7.6 Hz). MS: m/z 813 (M+H).

Example 8

Compound of formula 1: R²=R³=R⁷=H, R¹=3-(4-hydroxy-phenyl)-propyl

To a solution of 9-deoxy-9-hydroxyimino-11-deoxy-5-O-desosaminy-11-(3-(4-hydroxy-phenyl)-propyl)hydrazo-6-O-methyl-3-oxoerythronolide A, 11,12-carbamate (formula 2, R₁=H, R₂=3-(4-hydroxy-phenyl)-indol-propyl) (24 mg, 0.03 mmol) in CHCl₃ (1 mL) was added 37%
30 aqueous CH₂O (12 μL) followed by HCO₂H (11 μL). The resulting solution was heated at 65°C for 2 hours. The reaction was diluted with saturated NaHCO₃, and CH₂Cl₂ was added. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The
35 residue was purified by preparative TLC (89% CH₂Cl₂-9% MeOH-1% NH₃•H₂O) to afford the title compound as a white solid.

¹H NMR (400 MHz, CDCl₃) δ: 6.96 (2H, d, J = 8.4 Hz), 6.68 (2H, d, J = 8.4 Hz), 5.47 (1H, d, J = 14.8 Hz), 4.95 (1H, dd, J = 2.4 and 10.8 Hz), 4.78 (1H, d, J = 14.8 Hz), 4.34 (1H, d, J = 7.6 Hz), 4.27 (1H, d, J = 7.2 Hz), 3.98 (1H, s), 3.84 (1H, q, J = 7.2 Hz), 3.18 (1H, dd, J = 7.2 and 10.4 Hz), 2.80 (3H, s), 2.26 (6H, s), 1.52 (3H, s), 1.46 (3H, s), 1.35 (3H, d, J = 6.4 Hz), 1.31 (3H, d, J = 6.4 Hz), 1.30 (3H, d, J = 6.4 Hz), 1.23 (3H, d, J = 6.0 Hz), 0.99 (3H, d, J = 7.2 Hz), and 0.83 (3H, t, J = 7.2 Hz).

MS: m/z 789 (M+H).

Example 9

Compound of formula 1: R²=R³=R⁷=H, R¹=3-(1H-indol-3-yl)-propyl

10 To a solution of 9-deoxo-9-hydroxyimino-11-deoxy-5-O-desosaminy-11-(3-(1H-indol-3-yl)-propyl)hydrazo-6-O-methyl-3-oxoerythronolide A, 11,12-carbamate (formula 2, R₁=H, R₂=3-(1H-indol-3-yl)-propyl) (15 mg, 0.02 mmol) in CHCl₃ (1 mL) was added 37% aqueous CH₂O (8 μL) followed by HCO₂H (7 μL). The resulting solution was heated at 65°C for 2 hours. The reaction was diluted with saturated NaHCO₃, and CH₂Cl₂ was added. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by preparative TLC (89% CH₂Cl₂-9% MeOH-1% NH₃•H₂O) to afford the title compound as a white solid.

20 ¹H NMR (400 MHz, CDCl₃) δ: 7.54 (1H, d, J = 7.6 Hz), 7.44 (1H, d, J = 8.0 Hz), 7.17 (1H, t, J = 7.2 Hz), 7.09 (1H, t, J = 6.8 Hz), 6.99 (1H, s), 5.57 (1H, br. s), 5.43 (1H, d, J = 14.8 Hz), 4.86 (1H, dd, J = 2.4 and 10.8 Hz), 4.76 (1H, d, J = 14.8 Hz), 4.23 (1H, d, J = 7.2 Hz), 4.22 (1H, d, J = 8.4 Hz), 3.89 (1H, s), 3.79 (1H, q, J = 6.8 Hz), 3.16 (1H, dd, J = 7.2 and 10.4 Hz), 2.44 (3H, s), 2.25 (6H, s), 1.50 (3H, s), 1.36 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.8 Hz), 1.26 (3H, d, J = 8.0 Hz), 1.21 (3H, d, J = 6.0 Hz), 0.96 (3H, d, J = 7.2 Hz) and 0.81 (3H, t, J = 7.2 Hz).

25 MS: m/z 812 (M+H).

Example 10

Compound of formula 1: R²=R³=R⁷=H, R¹=3-(4-pyridin-3-yl-imidazol-1-yl)-propyl

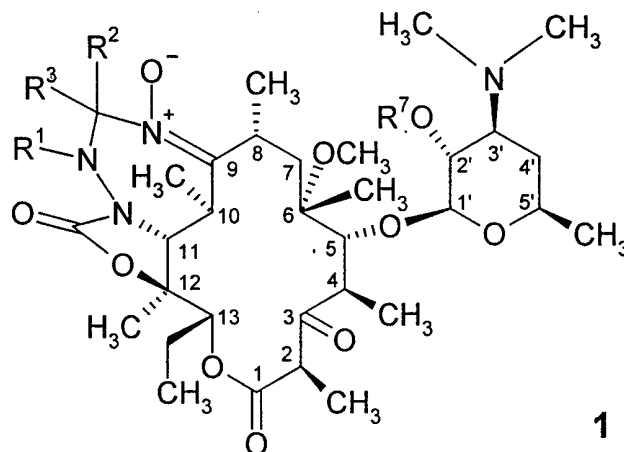
30 To a solution of 9-deoxo-9-hydroxyimino-11-deoxy-5-O-desosaminy-11-(3-(4-pyridin-3-yl-imidazol-1-yl)-propyl)hydrazo-6-O-methyl-3-oxoerythronolide A, 11,12-carbamate (formula 2, R⁷=H, R¹=3-(4-pyridin-3-yl-imidazol-1-yl)propyl) (231 mg, 0.28 mmol) in CHCl₃ (4 mL) was added 37% aqueous CH₂O (110 μL) followed by HCO₂H (100 μL). The resulting solution was heated at 65°C for 2 hours. The reaction was diluted with saturated NaHCO₃, and CH₂Cl₂ was added. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by preparative TLC (89% CH₂Cl₂-9% MEOH-1% NH₃•H₂O) to afford the title compound as a white solid.

^1H NMR (400 MHz, CDCl_3) δ : 8.93 (1H, d, $J = 2.0$ Hz), 8.43 (1H, dd, $J = 1.2, .4$ Hz), 8.04 (1H, dt, $J = 1.6, 7.6$ Hz), 7.56 (1H, s), 7.31 (1H, s), 7.24 (1H, dd, $J = 4.0, 6.4$ Hz), 5.52 (1H, d, $J = 14.4$ Hz), 4.85 (1H, d, $J = 10.8$ Hz), 4.71 (1H, d, $J = 14.8$ Hz), 4.32 (1H, d, $J = 7.6$ Hz), 4.21 (1H, t, $J = 6.8$ Hz), 4.01 (1H, m), 3.93 (1H, s), 3.83 (1H, q, $J = 6.8$ Hz), 2.75 (3H, s), 2.58 (6H, s), 1.33 (6H, d, $J = 7.2$ Hz), 1.27 (3H, d, $J = 6.0$ Hz), 1.25 (3H, d, $J = 6.2$ Hz), 1.00 (3H, d, $J = 7.2$ Hz), and 0.81 (3H, d, $J = 7.2$ Hz).

MS: m/z 840 ($M+H$).

What is claimed is:

1. A compound of the formula



- 5 and pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from H, $-(CR^4R^5)_mR^6$, $-C(O)(CR^4R^5)_mR^6$, $-C(O)O(CR^4R^5)_mR^6$, $-C(O)NR^4(CR^4R^5)_mR^6$, wherein m is an integer ranging from 0 to 6 and both R^4 and R^5 may vary for each iteration where m is greater than 1;

- 10 each R^2 and R^3 are independently selected from H and C_1 - C_{18} alkyl, wherein one or two carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N, and are optionally substituted by 1 to 3 substituents independently selected from the group consisting of $-C(O)O(C_1-C_{10})$ alkyl, $-O(C_1-C_{10})$ alkyl, C_1 - C_{10} alkanoyl, halo, nitro, cyano, C_1 - C_{10} alkyl, 4-10 membered heterocyclic, C_6 - C_{10} aryl, $-NH(C_1-C_{10})$ alkyl, $-S(C_1-C_{10})$ alkyl, $-SO(C_1-C_{10})$ alkyl, $-SO_2(C_1-C_{10})$ alkyl and $-SO_2N(C_1-C_{10})$ alkyl, provided that two O atoms, two S atoms or an S and
15 an O atom are not bonded to each other;

each R^4 and R^5 are independently selected from H, halo and C_1 - C_6 alkyl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and each R^4 and R^5 may vary independently when m is greater than 1, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other; or

- 20 each R^4 and R^5 taken together with the carbon to which they are attached can form a 3-10 membered ring, wherein one or more carbons of said ring are optionally replaced by a heteroatom selected from O, S and N, and are optionally substituted by 1 to 3 substituents independently selected from the group consisting of $-C(O)O(C_1-C_{10})$ alkyl, $-O(C_1-C_{10})$ alkyl, C_1 - C_{10} alkanoyl, halo, nitro, cyano, C_1 - C_{10} alkyl, 4-10 membered heterocyclic, C_6 - C_{10} aryl, $-NH(C_1$ -
25 $C_{10})$ alkyl, $-N((C_1-C_{10})alkyl)_2$, $-S(C_1-C_{10})$ alkyl, $-SO(C_1-C_{10})$ alkyl, $-SO_2(C_2(C_1-C_{10})alkyl)$ and $-SO_2N(C_1-C_{10})$ alkyl, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other;

R⁶ is (C₁-C₁₈)alkyl, a 4-10 membered heterocyclic or C₆-C₁₀ aryl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and said heterocyclic and aryl groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of -C(O)O(C₁-C₁₀)alkyl, -O(C₁-C₁₀)alkyl, C₁-C₁₀ alkanoyl, halo, nitro, cyano, (C₁-C₁₀) alkyl, -NH(C₁-C₁₀)alkyl, -N((C₁-C₁₀)alkyl)₂, -S(C₁-C₁₀)alkyl, -SO(C₁-C₁₀)alkyl, -SO₂(C₁-C₁₀)alkyl and -SO₂N(C₁-C₁₀)alkyl, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other; and

R⁷ is H, -C(O)O(C₁-C₁₈)alkyl or -C(O)(C₁-C₁₈)alkyl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and wherein in the alkyl portion of said alkanoyl one or two carbons optionally may be replaced by a heteroatom selected from O, S and N, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other.

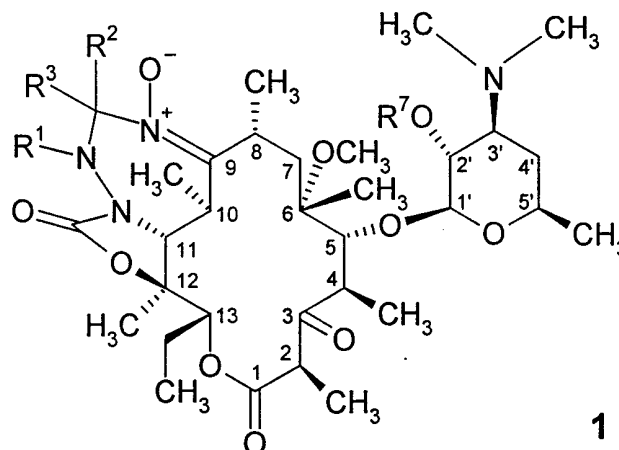
2. The compound of claim 1 wherein R⁷ is H.
3. The compound of claim 1 wherein R³ is H.
- 15 4. The compound of claim 1 wherein R³=R²=H.
5. The compound of claim 1 wherein R³=R²=R⁷=H.
6. The compound of claim 1 wherein R¹ is (CH₂)_mR⁶, wherein m is an integer ranging from 0 to 6.
7. The compound of claim 6 wherein R⁶ is selected from the group consisting of:
 - 20 quinolin-4-yl, quinolin-5-yl, quinolin-8-yl, 4-phenyl-1-imidazol-1-yl, 4-pyridin-3-yl-imidazol-1-yl and imidazo(4,5-b)pyridin-3-yl.
8. The compound of claim 6 wherein m is 3.
9. The compound of claim 8 wherein R⁶ is selected from the group consisting of:
 - 25 imidazo(4,5-b)pyridin-3-yl.
10. The compound of claim 1 selected from the group consisting of:
 - the compound of formula 1 wherein R⁷=H, R³=R²=H, R¹=3-quinolin-4-yl-propyl;
 - the compound of formula 1 wherein R⁷=H, R³=R²=H, R¹=7-methoxy-quinolin-4-yl-propyl;
 - the compound of formula 1 wherein R⁷=H, R³=R²=H, R¹=3-benzoimidazol-1-yl-propyl;
 - 30 the compound of formula 1 wherein R⁷=H, R³=R²=H, R¹=3-indol-1-yl-propyl;
 - the compound of formula 1 wherein R⁷=H, R³=R²=H, R¹=3-indazol-1-yl-propyl;
 - the compound of formula 1 wherein R⁷=H, R³=R²=H, R¹=3-carbazol-1-yl-propyl;
 - the compound of formula 1 wherein R⁷=H, R³=R²=H, R¹=3-(5-phenyl-1H-pyrrol-2-yl)-propyl;
 - the compound of formula 1 wherein R⁷=H, R³=R²=H, R¹=3-(4-phenyl-imidazol-1-yl)-propyl;
 - 35 the compound of formula 1 wherein R⁷=H, R³=R²=H, R¹=3-(imidazo(4,5-b)pyridin-3-yl)-propyl;
 - the compound of formula 1 wherein R⁷=H, R³=R²=H, R¹=3-(4-pyridin-3-yl-imidazol-1-yl)-propyl;

- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3-(3-(4\text{-chlorophenyl})-(1,2,4)\text{oxadiazol-5-yl})\text{-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3-(3-(4\text{-methoxyphenyl})-(1,2,4)\text{oxadiazol-5-yl})\text{-propyl}$;
- 5 the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3-(3-(4\text{-pyridin-4-yl})-(1,2,4)\text{oxadiazol-5-yl})\text{-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-benzotriazol-1-yl-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-benzotriazol-2-yl-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-(1H-indol-3-yl)-propyl}$;
- 10 the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-pyridin-4-yl-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-pyridin-3-yl-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-pyridin-2-yl-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-phenylpropyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-(2-methoxyphenyl)-propyl}$;
- 15 the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-furan-2-yl-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-thiophen-2-yl-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-thiophen-2-yl-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-pyrrol-1-yl-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-(2-pyridin-3-yl-thiazol-4-yl)-propyl}$;
- 20 the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-(2-phenyl-thiazol-5-yl)-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-(2-phenyl-thiazol-5-yl)-propyl}$;
- the compound of formula 1 wherein $R^7=H$, $R^3=R^2=H$, $R^1=3\text{-(4-phenyl-1H-imidazol-2-yl)-propyl}$; and pharmaceutically acceptable salts of the foregoing compounds.

11. A pharmaceutical composition for the treatment of a bacterial infection or
25 protozoa infection in a mammal, fish, or bird which comprises a therapeutically effective amount
of a compound of formula 1 as defined in claim 1, or a pharmaceutically acceptable salt thereof,
and a pharmaceutically acceptable carrier.

12. A method of treating a bacterial infection or a protozoa infection in a mammal,
fish, or bird which comprises administering to said mammal, fish, or bird a therapeutically
30 effective amount of a compound of formula 1 as defined in claim 1.

13. A method of preparing a compound of the formula



and pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from H, $-(CR^4R^5)_mR^6$, $-C(O)(CR^4R^5)_mR^6$, $-C(O)O(CR^4R^5)_mR^6$,

- 5 $-C(O)NR^4(CR^4R^5)_mR^6$, wherein m is an integer ranging from 0 to 6 and both R^4 and R^5 may vary for each iteration where m is greater than 1;

each R^2 and R^3 are independently selected from H and C_1 - C_{18} alkyl, wherein one or two carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N, and are optionally substituted by 1 to 3 substituents independently selected from the group consisting of

10 $-C(O)O(C_1-C_{10})$ alkyl, $-O(C_1-C_{10})$ alkyl, C_1 - C_{10} alkanoyl, halo, nitro, cyano, C_1 - C_{10} alkyl, 4-10 membered heterocyclic, C_6 - C_{10} aryl, $-NH(C_1-C_{10})$ alkyl, $-S(C_1-C_{10})$ alkyl, $-SO(C_1-C_{10})$ alkyl, $-SO_2(C_1-C_{10})$ alkyl and $-SO_2N(C_1-C_{10})$ alkyl, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other;

each R^4 and R^5 are independently selected from H, halo and C_1 - C_6 alkyl, wherein 1 to 3

15 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and each R^4 and R^5 may vary independently when m is greater than 1, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other; or

each R^4 and R^5 taken together with the carbon to which they are attached can form a 3-

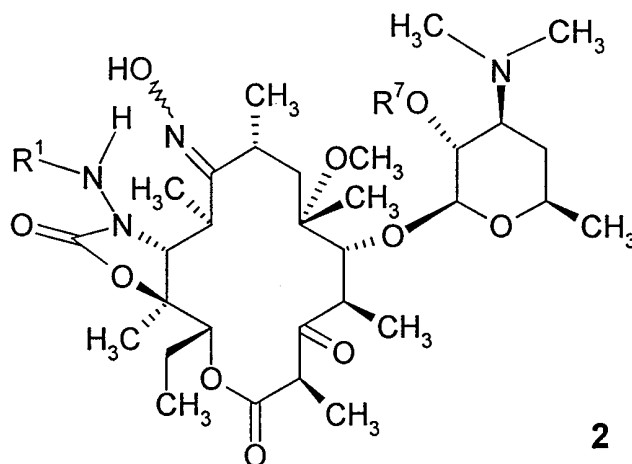
20 10 membered ring, wherein one or more carbons of said ring are optionally replaced by a heteroatom selected from O, S and N, and are optionally substituted by 1 to 3 substituents independently selected from the group consisting of $-C(O)O(C_1-C_{10})$ alkyl, $-O(C_1-C_{10})$ alkyl, C_1 - C_{10} alkanoyl, halo, nitro, cyano, C_1 - C_{10} alkyl, 4-10 membered heterocyclic, C_6 - C_{10} aryl, $-NH(C_1-C_{10})$ alkyl, $-N((C_1-C_{10})alkyl)_2$, $-S(C_1-C_{10})$ alkyl, $-SO(C_1-C_{10})$ alkyl, $-SO_2(C_2(C_1-C_{10})alkyl)$ and $-SO_2N(C_1-C_{10})$ alkyl, provided that two O atoms, two S atoms or an S and an O atom are not

25 bonded to each other;

R^6 is (C_1-C_{18}) alkyl, a 4-10 membered heterocyclic or C_6 - C_{10} aryl, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and said

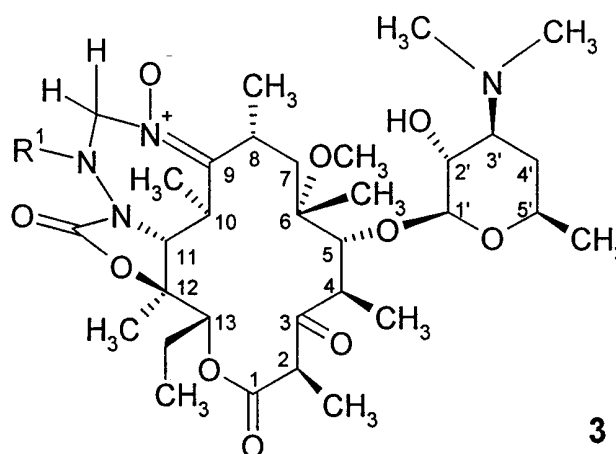
heterocyclic and aryl groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of $-C(O)O(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, C_1-C_{10} alkanoyl, halo, nitro, cyano, $(C_1-C_{10}) alkyl$, $-NH(C_1-C_{10})alkyl$, $-N((C_1-C_{10})alkyl)_2$, $-S(C_1-C_{10} alkyl)$, $-SO(C_1-C_{10})alkyl$, $-SO_2(C_1-C_{10})alkyl$ and $-SO_2N(C_1-C_{10})alkyl$, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other; and

R^7 is H, $-C(O)O(C_1-C_{18})alkyl$ or $-C(O)(C_1-C_{18})alkyl$, wherein 1 to 3 carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and wherein in the alkyl portion of said alkanoyl one or two carbons optionally may be replaced by a heteroatom selected from O, S and N, provided that two O atoms, two S atoms or an S and an O atom are not bonded to each other, which comprises treating a compound of the formula



wherein R^7 and R^1 are as defined above, with a compound of the formula $R^3R^2C=O$, wherein R^3 and R^2 are as defined for the compound of formula 1, in the presence of an acid.

14. The method of claim 13 wherein the compound of the formula $R^3R^2C=O$ is CH_2O .
15. The method of claim 13 wherein the acid is selected from the group consisting of: suitable acids include, for example, acetic acid, formic acid, para-toluene sulfonic acid and propionic acid.
16. A compound of the formula



and pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from H, $-(CR^4R^5)_mR^6$, $-C(O)(CR^4R^5)_mR^6$, $-C(O)O(CR^4R^5)_mR^6$,

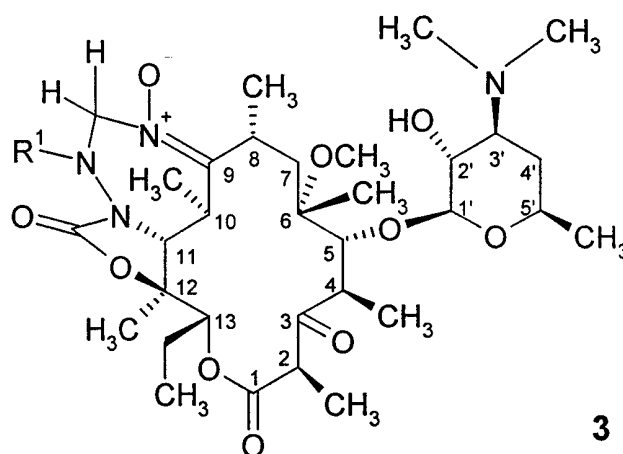
$-C(O)NR^4(CR^4R^5)_mR^6$, wherein m is an integer ranging from 0 to 6 and both R^4 and R^5 may vary
5 for each iteration where m is greater than 1;

each R^4 and R^5 are independently selected from H, halo and C_1 - C_6 alkyl, wherein 1 to 3
carbons of said alkyl are optionally replaced by a heteroatom selected from O, S and N and each
 R^4 and R^5 may vary independently when m is greater than 1, provided that two O atoms, two S
atoms or an S and an O atom are not bonded to each other; or

10 each R^4 and R^5 taken together with the carbon to which they are attached can form a 3-
10 membered ring, wherein one or more carbons of said ring are optionally replaced by a
heteroatom selected from O, S and N, and are optionally substituted by 1 to 3 substituents
independently selected from the group consisting of $-C(O)O(C_1-C_{10})$ alkyl, $-O(C_1-C_{10})$ alkyl, C_1-C_{10}
alkanoyl, halo, nitro, cyano, C_1-C_{10} alkyl, 4-10 membered heterocyclic, C_6-C_{10} aryl, $-NH(C_1-$
15 $C_{10})$ alkyl, $-N((C_1-C_{10})alkyl)_2$, $-S(C_1-C_{10})$ alkyl, $-SO(C_1-C_{10})$ alkyl, $-SO_2(C_2(C_1-C_{10})alkyl)$ and $-$
 $SO_2N(C_1-C_{10})$ alkyl, provided that two O atoms, two S atoms or an S and an O atom are not
bonded to each other; and

R^6 is (C_1-C_{10}) alkyl, a 4-10 membered heterocyclic or C_6-C_{10} aryl, wherein 1 to 3 carbons
of said alkyl are optionally replaced by a heteroatom selected from O, S and N and said
20 heterocyclic and aryl groups are optionally substituted by 1 to 3 substituents independently
selected from the group consisting of $-C(O)O(C_1-C_{10})$ alkyl, $-O(C_1-C_{10})$ alkyl, C_1-C_{10} alkanoyl, halo,
nitro, cyano, (C_1-C_{10}) alkyl, $-NH(C_1-C_{10})$ alkyl, $-N((C_1-C_{10})alkyl)_2$, $-S(C_1-C_{10})$ alkyl,
 $-SO(C_1-C_{10})$ alkyl,
 $-SO_2(C_1-C_{10})$ alkyl and $-SO_2N(C_1-C_{10})$ alkyl, provided that two O atoms, two S atoms or an S and
an O atom are not bonded to each other.

25 17. A compound of the formula



and pharmaceutically acceptable salts thereof, wherein:

R¹ is selected from the group consisting of: phenylbutyl, 3-quinolin-4-yl-propyl, 3-(4-phenyl-imidazol-1-yl)-propyl, 3-(2-methoxyphenyl)-propyl, 3-furan-2-yl-propyl, 3-benzoimidazol-
5 1-yl-propyl, 3-indazol-1-yl-propyl, 3-(4-hydroxy-phenyl)-propyl, 3-(1H-indol-3-yl)-propyl, and 3-(4-pyridin-3-yl-imidazol-1-yl)-propyl.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 99/00855

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07H17/08 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 17356 A (ABBOTT LAB) 15 May 1997 (1997-05-15) abstract; claims 1-17 ---	1,11-13
A	FR 2 732 023 A (ROUSSEL UCLAF) 27 September 1996 (1996-09-27) abstract ---	1,11-13
A	EP 0 638 585 A (TAISHO PHARMA CO LTD) 15 February 1995 (1995-02-15) abstract; claim 1 ---	1,11-13
P,A	WO 99 21865 A (WU YONG JIN ;PFIZER PROD INC (US)) 6 May 1999 (1999-05-06) the whole document ---	1-17
	-/--	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

13 August 1999

Date of mailing of the international search report

23/08/1999

Name and mailing address of the ISA
 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Scott, J

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/IB 99/00855

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO 99 21866 A (WU YONG JIN ; PFIZER PROD INC (US)) 6 May 1999 (1999-05-06) the whole document -----	1-17

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/00855

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 99/00855

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9717356 A	15-05-1997	AU 7447096 A	29-05-1997
		EP 0876388 A	11-11-1998

FR 2732023 A	27-09-1996	NONE	

EP 0638585 A	15-02-1995	AU 4022393 A	18-11-1993
		DE 69305987 D	19-12-1996
		DE 69305987 T	06-03-1997
		GR 3021992 T	31-03-1997
		US 5631355 A	20-05-1997
		AT 135707 T	15-04-1996
		AT 145212 T	15-11-1996
		AU 4022293 A	18-11-1993
		CA 2118488 A	23-10-1993
		CA 2118489 A	23-10-1993
		DE 69301916 D	25-04-1996
		DE 69301916 T	08-08-1996
		DK 638584 T	15-04-1996
		DK 638585 T	02-12-1996
		EP 0638584 A	15-02-1995
		ES 2087737 T	16-07-1996
		ES 2096915 T	16-03-1997
		GR 3019787 T	31-07-1996
		JP 6009678 A	18-01-1994
WO 9321199 A	28-10-1993		
WO 9321200 A	28-10-1993		
US 5591837 A	07-01-1997		

WO 9921865 A	06-05-1999	AU 9277398 A	17-05-1999

WO 9921866 A	06-05-1999	AU 9277698 A	17-05-1999
